High Impact Physical Activity and Bone Health of Lower Extremities in Childhood Cancer Survivors: A Cross-sectional Study of SURfit

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Brief description

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Childhood cancer survivors (CCS) are at risk of poor bone health. The potential benefits of high impact loading physical activity (IL-PA) on bone health in CCS are still poorly understood. We found indication that bone health in young CCS can benefit from higher daily duration and number of IL-PA. Our results are promising since performing just a few minutes of IL-PA daily could be a simple and feasible measure to promote bone health in CCS.

Abbreviations

cort vBMD	Cortical volumetric bone mineral density (mg/cm^3)
CPM	Counts per minute (counts/minute), indicator for PA
DXA	Dual-energy X-ray absorptiometry
FN	Femoral neck
IL	Impact loading
IL-PA	Impact loading physical activity
IPD	Impact Peak Duration: Daily minutes spent in impact loading >2 g based on triaxial data whereby ≥144 counts/second represent activities ≥2 g based on ground reaction force [1]
IPN	Impact Peak Number: Daily number of vertical impact peaks per hour >2 g based on gravity corrected raw acceleration data (100Hz)
LS	Lumbar spine
MVPA	Moderate to vigorous physical activity
PA	Physical activity
pQCT	Peripheral quantitative computed tomography
SSI	Strain strength index (mm^3)
TH	Total Hip
total CSA	Total cross-sectional area (mm^2)
total vBMD	Total volumetric bone mineral density (mg/cm^3)
trab vBMD	Trabecular volumetric bone mineral density (mg/cm^3)

Abstract

Childhood cancer survivors (CCS) are at risk of reduced bone health and premature osteoporosis. As physical activity with high impact loading (IL-PA) is known to promote bone health, we compared bone densitometry and microstructure between groups of CCS who performed different amounts of physical activities in their daily life. We used baseline data of a single-centre PA trial including 161 CCS from the Swiss Childhood Cancer Registry, aged <16 at diagnosis, ≥16 at study, and ≥5 years since diagnosis. Lower body bone health was assessed with peripheral quantitative computed tomography (pQCT) and dual-energy X-ray absorptiometry (DXA). Daily IL-PA (duration in activities >2 g acceleration and numbers of vertical impacts/hour >2 g) was captured using hip-worn accelerometers (1-3 weeks). For both IL-PA approaches, we formed low, middle, and high activity groups based on tertiles. Bone health of the high and middle active groups were compared to the low active group. 63% of CCS had indication of at least one bone mineral density z-score ≤-1 measured by pQCT or DXA. The high IL-PA group performing 2.8 min/day or 19.1 impact peaks/h >2 g (median) showed about 3-13% better microstructural and densitometric bone health as compared to the low IL-PA group with 0.38 min/day or 0.85 peaks/h >2 g. Just a few minutes and repetitions of high IL-PA as easily modifiable lifestyle factor may be

sufficient to improve bone health in adult CCS. Future longitudinal research is needed to better understand pattern and dosage of minimal impact loading needed to strengthen bone in growing and adult CCS.

Introduction

Childhood cancer survivors (CCS) are at risk for late effects such as premature osteoporosis and related fractures, which are associated with a significant individual, societal and economic burden [2-5]. This is partly explained by an impaired peak bone mass acquisition during cancer disease and therapy [3, 4]. In CCS, bone metabolism had been shown to be affected by side effects directly caused by cancer treatment (e.g. antimetabolites inhibit formation of new bone), by indirect cancer treatment effects (e.g. radiation-induced pituitary hormone dysfunction, growth hormone deficiency, and hypogonadism) or by the interfering effect of the cancer disease itself [3, 4, 6]. As in the general population and irrespective of disease, also genetics [3, 7, 8], lifestyle factors such as nutrition [8], smoking [4, 9], and physical activity (PA) [3, 8, 10] may influence bone health.

In health and disease, PA is an important and modifiable factor that promotes bone health and may decrease the risk of osteoporosis in later life [3, 4, 8, 10, 11]. Mechanical loading of bone can occur by bending or torsional forces through muscles [12-14], or by its compression through impact forces (jumping, running) [10, 15, 16]. As a consequence, individuals with a higher exposure to impact loading during daily life have better bone health, partly related and partly unrelated to greater muscle mass [1, 10, 11, 13, 14, 17]. Studies in the general population [10, 11, 17, 18], athletes [15, 16], and CCS [19] have shown that different ways of mechanical loading result in adaptive changes of bone that increase its mass, decrease its loss or improve its strength. Thereby, the osteogenic effect is dependent on magnitude, mode and rate of loading, the number of repetitions and duration, and the change of strain applied to the bone [10, 18, 20, 21]. Effects are most evident during growth but seem to persist during the life course [10].

The specific influence of impact loading (IL) to lower body densitometric and microarchitecture bone health has not been well elucidated in CCS. This cross-sectional study aimed to investigate the prevalence of low bone health (z-score $\leq$-1) in young adult CCS, and to determine the association between mechanical PA-related impact loading of daily living and bone mineral density as well as geometric bone parameters measured by peripheral quantitative computed tomography (pQCT) and dual-energy X-ray absorptiometry (DXA). We hypothesized that CCS with a higher exposure to impact loading during daily life have better bone health, irrespective of adjusting for potential confounding such as muscle mass and their previous cancer therapy.

Materials and methods

Study population

Data for this cross-sectional analysis were drawn from baseline assessments of the SURfit study (a randomized, controlled physical activity intervention for adult and adolescent survivors of childhood cancer, ClinicalTrials.gov identifier: NCT02730767) [22]. SURfit was a single-centre trial conducted at the University Children's Hospital Basel in Switzerland between September 2015 and February 2018. CCS identified in the Swiss Childhood Cancer Registry who were treated at a Swiss Paediatric Oncology clinic, aged ≥16 years at study, <16 years at diagnosis, and ≥5 years since the last cancer diagnosis were eligible. More detailed inclusion/exclusion criteria are described by Rueegg et al. (2017) [22]. 161 participants with initial baseline assessments in SURfit and at least one valid bone measurement were included (see **Supporting Information Figure S1)**. The study was approved by the Swiss Ethics Committee on research involving humans (Ethikkommission Nordwest- und Zentralschweiz [EKNZ]). Written informed consent was obtained from each survivor prior to participation in the study. Based on our a priori defined aim of teasing out health behaviours and health status of long-term CCS in Switzerland [22], we analysed the cross-sectional association between PA and bone health but without opening any information on group assignment.

Lower body bone health

Densitometric and microstructural bone health was measured by pQCT (XCT 2000; Stratec Medical, Pforzheim, Germany) and DXA (Discovery A densitometer; Hologic, Bedford, MA, USA). Quality assurance of both devices was checked, and if needed calibrated, before each measuring day according to manufacturers' guidelines. Volumetric bone mineral density (vBMD), bone mass, and bone geometry were measured using pQCT at the distal epiphysis (4%) and diaphysis (66%) of the tibia in the non-dominant lower leg [22]. A priori defined outcomes of interest were total and trabecular volumetric bone mineral density (mg/cm^3) [total and trab vBMD] at 4% of tibia length, cortical volumetric bone mineral density (mg/cm^3) [cort vBMD], total cortical cross-sectional area (mm^2) [total CSA], and strain strength index (mm^3) [SSI] at 66% tibia length. Z-scores could only be calculated for total and trab vBMD at 4% tibia based on available reference material [23, 24]. Outcomes by DXA included femoral neck (FN), total hip (TH), and lumbar spine (LS) areal BMD expressed in g/cm^2 and by age and gender matched z-scores [25]. For model adjustment purposes, muscle mass was defined as muscular cross-sectional area (mm²) at 66% tibia length by pQCT and total lean body mass by DXA.

Physical activity impact loading

PA was assessed by accelerometer using ActiGraph® GT3X+ (Pensacola, Florida, USA) worn between two baseline assessments 5-20 days apart. Participants were asked to wear the device 24 h/day on the right hip. It assessed accelerations with a frequency of 100Hz. Analysed time was restricted to activities between 06:00am to 10:00pm using the manufacturer's software (ActiLife 6.13.4). Participants with ≥4 days of ≥10 h/day wear time

[26, 27] during this time period were included. To investigate physical activity with high impact loading (IL-PA) potentially beneficial to bone the following two a priori defined types of PA evaluations were defined; **a)** daily minutes spent with impact loading >2 g (IPD) based on triaxial data whereby ≥144 counts per 1 s represented activities ≥2 g based on ground reaction force. IPD was calculated based on activity counts provided by the manufacturer's software using 1 s epochs, which is the shortest epoch length being supported. This approach was introduced and validated by Rowlands and Stiles [1] and is simple to use since count-based data can be directly processed by the commercially available software; **b)** number of impact peaks per hour >2 g (IPN) based on raw data and calculated using Python 3.7.0. The analysed vertical signal was corrected for gravity (high-pass filtering, 0.25 Hz). In this method, raw signals were selected as even 1 s epoch intervals used for IPD may not be sensitive enough to capture peaks of short, explosive activities such as jumping or fast running. Thus, IPD may underestimate IL due to smoothing of single peaks over 1 s interval. A graphic illustration for fast running can be found in **Figure 1** and a description of the algorithm in **Supporting Information Appendix 1**. In the Appendix, number of impact peaks between 1-2 g ($IPN_{(1\text{-}2g)}$) were further analysed. Both variables (IPD and IPN) were separately categorized into activity tertiles (low, middle, and high PA groups). Daily minutes spent in moderate to vigorous PA (MVPA) based on counts per minute (CPM) averaged across all valid days [28] were calculated for descriptive purposes using 60 s epoch data by ActiLife.

Covariates

Covariates (potential confounders for the associations between PA and bone health) selected a priori included muscle mass [13, 14], sex [3, 29], age [4, 8], height [29], age at primary cancer diagnosis [30], cumulative anthracycline doses using doxorubicin isotoxic equivalents [3, 4, 30, 31] and cumulative steroid doses using prednisone/dexamethasone dose ratios of 6.67 [3, 4, 30, 32], cranial radiation therapy ≥24 Gy [3, 4, 29, 33], and current smoking status (yes/no) [4, 9]. Clinical variables were extracted from medical records.

Statistical analysis

Descriptive analyses included median and interquartile range (IQR) for continuous and number and frequencies for categorical variables. Differences in bone densitometry and architecture across IL-PA groups were determined using (multivariable) linear regression (Beta coefficients [Beta] with 95% confidence intervals [95%CI]). Additionally, log-level regression (data not shown in detail) was used to describe approximate relative differences. Differences across IL-PA groups were analysed using three models for each bone health outcome according to IPD and IPN: a) without adjustment, b) adjusted for muscle mass, c) adjusted for all other covariates defined above. Regression diagnostics were performed graphically. Data analyses and graphical plotting were performed using R 3.5.0 [34]. Participants with <4 days of valid accelerometer data, missing or invalid bone measurements, or missing covariates were excluded from the specific group analyses.

Data availability

Data will be made available upon reasonable request.

Results

Characteristics of 161 included CCS are shown in **Table 1**. For final analyses, 11 participants had <4 days of valid accelerometer measurements and one participant was a wheelchair user and thus excluded (see study flow diagram provided in **Supporting Information Figure S1)**. Accelerometers were worn on average over 11 days (IQR; 8 to 13 days) with a median wear time of 14.2 hours/day (IQR; 13.5 to 15.1). Mean time spent in MVPA was 39 min per day (IQR; 26 to 53). Participants spent 1.2 min daily in IPD (IQR; 0.6 to 2.3), and exposed their bones with 3.9 peaks/h in IPN (IQR; 1.3 to 11.2).

Our cohort showed low bone health (BMD z-scores ≤-1) in nearly all examined locations (**Table 2**). About 56% of females and 70% of males showed low bone health at any site measured by pQCT or DXA. Nearly a third of females and half of males showed a low lumbar spine BMD z-score. 19% of females and 34% of males showed low bone health in both measurements (pQCT and DXA). Further information on densitometric and microstructural bone measurements can be found in the appendix (**Supporting Information Table S1**).

As shown in **Figure 2**, we found a consistent tendency in most parameters towards improved bone health parameters in the group of the highest tertile of daily IPD or IPN compared to the lowest tertile. Differences in densitometric and microstructural measures between these groups ranged from 3-13% (adjusted for all covariates) and were significantly higher for most trabecular, cortical or mixed bone measures of hip and tibia, except for cortical BMD at 66% and BMD at lumbar spine. Model adjustments for muscle mass or covariate adjustments (**Figure 2**) reduced effect sizes in the majority of models but did not change the conclusion. Weaker and mostly non-significant differences in bone parameters were seen between the middle and the lowest impact group for IPD and IPN. Additional analyses with wear-time adjustment did not change the interpretation. **Table 3** shows demographic and clinical characteristics for the low, middle, and high tertile group according to Rowlands and Stiles[1] (IPD), which is calculated with the commercially available and often used software ActiLife. **Supporting information Table S2** provides the same characteristics stratified by IPN. There was no major difference in clinical and demographic characteristics potentially affecting bone health among different loading groups except for smokers that were less prevalent in the high active tertile.

The comparison of tertile groups for lower intense impact loading of 1-2 g showed a similar trend than for the higher impact loadings >2 g (IPD and IPN) for some bone parameters (see **Supporting Information Tables S3 to S4)**. Adjusting these analyses for IL-PA duration or peaks >2 g reduced the effect sizes and almost all significant effects were lost.

In addition, association between densitometric and microstructural bone measurements and muscle mass were calculated (without any adjustment). For pQCT measurements, association between muscle mass and tot/trab

vBMD at tibia 4% were low and non-significant (Beta=0.0052, p=0.055, and Beta=0.0045, p=0.066). Statistically significant associations between muscle mass and bone were found for cort vBMD (Beta=-0.011, p<0.001), tot CSA (Beta=0.024, p<0.001), and SSI (Beta= 0.24, p<0.001). For DXA measurements, the following associations with muscle mass were found; FN (Beta= 0.022, p=0.0030), TH (Beta=0.017, p=0.012), and LS (Beta 0.0051, p=0.57).

Discussion

In this cross-sectional study, more physically active CCS (high duration and frequency of impact loadings >2 g) showed approximately 3-13% better lower body cortical geometry, bone strength and mainly better trabecular bone density compared to their less active counterparts. This was irrespective of method used to assess impact loading (IPD or IPN) and model adjustment in a group at risk for low bone health. Differences between activity groups and bone properties remained after controlling for muscle mass, previous tumour therapy, age at therapy, sex, height, current age and smoking status, although effect sizes got smaller with model adjustments for potential confounders. Although one has to be carefully in interpreting these findings due to the cross-sectional nature of the study and the large confidence intervals, they are relevant from a public health perspective as they demonstrate that a modifiable lifestyle factor in form of just a few minutes of feasible impact loading of the lower body can potentially improve bone health in a population at risk.

Childhood cancer patients are at risk for musculoskeletal morbidity including low BMD that may persist after therapy [3, 4, 30]. Prevalence of low z-scores ≤-1 by DXA was substantial in both genders, and comparable to similar study populations [35, 36]. Moreover, low DXA z-scores were prevalent irrespective of factors that can strongly influence measurement errors [37, 38] such as height, age or sex. Especially low height can lead to an overestimation of prevalence in low BMD by DXA [37, 38]. In our study, these variables were equally distributed among the low and the normal BMD groups. 19% of females and 34% of males showed low BMD in both pQCT and DXA at any measurement site, while more than half of the participants showed low BMD on at least one measurement site by pQCT or DXA. This low agreement of methods is known and generally referred to their different techniques of data acquisition, as well as the fact that they measure different properties of bone at different regions of interest [37, 38]. Although the joined use of both methods allowed to combine their individual strengths and minimized their limitations, discrepancies in findings among these methods have to be carefully interpreted.

Among preventive strategies, a physically active lifestyle has been shown to increase bone health in the general population and likewise in CCS [3, 4, 10, 11, 19]. Preserving bone mass and structure in adulthood potentially requires high-IL-PA [10, 17, 18]. Vainionpaa *et al.* [17] reported that less than 100 vertical accelerations peaks per day >3.9 g were associated with increased BMD of the hip in premenopausal women. In our study, a higher regular exposure to IL, irrespective of analysis approach was associated with improved densitometric and microstructural bone parameters. A similar but weaker trend for some bone parameters was also found for lower intense IL-PA exposures between 1-2 g. However, when adjusting these analyses for IL-PA >2 g markedly lowered the effect sizes and increased the p-values (mostly non-significant after adjustment). This may indicate that higher duration and amount of peaks spent in IL-PA between 1-2 g may not be equally effective for lower body bone health compared to higher IL-PA >2 g. Based on our analyses we are not able to provide information

about the optimal IL-PA cut-off point, but bone-beneficial effects may already occur at lower IL-PA. Stiles *et al*. [18] discovered that more than one minute/day spent in PA above 1 g was already positively associated with bone health in premenopausal women. As there is a greater potential for bone adaptations in the growing skeleton, studies in growing CCS and young women could indeed show that already lower magnitude (high frequency) stimulations comparable <1 g applied regularly over a year (20 min daily for one year) may have a positive effect on bone [19, 39]. Common in all these studies is the feature that IL contributed to bone health in various populations.

Differences in bone measurements among young adult CCS in this study were likely and at least in part due to differences in physically active lifestyle. Following these lines, young soccer players for instance showed a higher BMD, larger cortical geometry, and larger trabecular microstructure of weight-bearing bones than non-athletic controls [15]. Previous gymnasts as young adults typically show a dual pattern of bony adaptations to loading by adaptation of bone shape (larger circumference and cortical CSA) in the shaft and magnification of bone density (trab BMD) at epiphyses [16]. Our data nicely fit this picture; the high compared to the low impact group showed increased trabecular BMD at the distal tibia, and an enlarged cortical area as a consequence of bone adaption, leading to more robust bone with a better SSI. Although we can only speculate based on our cross-sectional data, the geometry with higher bone CSA in the tibial shaft of the high active group suggests that increased loading has also taken place during growth as shown in vivo unilateral loading model of racket ball athletes [40]. To control for potential clinical factors of the past and present that may have contributed to low bone health, we adjusted our models for important confounders that took off some, but not all of the strength of association between IL and bone. Furthermore, CCS characteristics across PA groups that may have affected bone development or maintenance such as growth or pubertal retardation, menstrual disturbances, or hormonal treatments suggestive for previous deficits were generally comparable. Nevertheless, the higher smoking frequency (models were adjusted for smoking) in the lowest PA group may be indicative of other unfavourable lifestyle behaviours (e.g. alcohol consumption or nutrition) that may also have contributed to different bone outcomes [4, 8, 9]. The lack of association between LS and IL is hard to interpret and may have diagnostic or mechanical explanations with low precision of DXA [37, 38] and/or higher demands of IL-PA needed for positive effect on LS [41] that are usually not achieved during normal recreational sports as done in our cohort [1, 10].

From a practical point of view, our accelerometer measurements can be easily translated into daily life. Performing sports such as fast running, drop jumps or jumping with countermovement usually result in high impacts >2 g and these activities may even reach forces of 3.9 g in magnitude (as shown in **Figure 1**). In contrast, activities like stepping or lateral jumping ($IPN_{1\text{-}2g}$) or slow and brisk walking ($IPN_{<1g}$) are beneficial to cardiovascular and metabolic health outcomes [10], but may indeed be too low to promote bone health [1, 10, 17].

Strength and limitations

Strengths of this study is the novel objective measurement of daily PA by accelerometer including raw data, which ideally captures short activity impacts [1]. To our knowledge, a comparable approach that associates mechanical loading to bone health in CCS has never been used before. In our two approaches used to measure IL-PA, there was a moderate agreement regarding participant's categorisation to the different activity groups between IPD and IPN. Our introduced IPN approach to measure IL-PA is promising for future studies because it has advantages in capturing short, explosive activities potentially beneficial to bone health. Moreover, most research that looked at bone health in CCS used DXA, and only few applied pQCT measurements. Both measurement methods are radiologic surrogate measures of bone strength [3, 42, 43] and both have their own technical limitations, but provided evidence that bone properties as well as its geometry were associated with IL-PA. DXA is unable to measure true volumetric density and its results are prone to various methodological errors due to different bone and body size, rotational inaccuracies, or inhomogeneity and ratio variation of the surrounding fat/lean tissue [37, 38]. In contrast, pQCT does not show these disadvantages and permits an unambiguous distinction between cortical and trabecular bone, and BMD [43]. Its limitations contain the lack of standardized measurements and analyses and its sensitivity to positional and movement variations [38]. Limitations of this study are related to the cross-sectional design precluding causality and the possibility of selection bias. Due to sample size, we could not consider further factors for model adjustment (e.g. functional limitations). Further, we did not show all results for model covariates of potential clinical interest or perform subgroup analyses (e.g. tumour type and therapy, age at diagnosis, endocrinopathies). The sampling frequency of accelerometers was set to 100Hz to be comparable with the method provided by our reference group [1], which differs from the default of 30, 60 or 90 Hz for which the manufacturer's algorithm has been optimized [44]. Thus, differences to studies using other sampling frequencies may arise. Additionally, high intensity activity may be filtered out when using processed epoch data, and thus, may affect the conversion from raw signals to counts [44]. We also assumed that our accelerometer measures represented a constant PA pattern of individuals over the last years, which may not be the case.

Conclusion

We found indication that a longer time and higher amount of daily IL-PA (like fast running or jumping) was associated with better bone health in CCS irrespective of adjustments for demographic, behavioural and treatment related factors. The highest among IL-PA groups performing in median 2.8 min/day or 19.1 impact peaks/h >2 g showed about 3-13% better microstructural and densitometric bone health as compared to the lowest IL-PA group with 0.38 min/day or 0.85 peaks/h >2 g. From a public health perspective, our results are promising since reaching higher daily impact loading of about 3 minutes duration or roughly 300 impact repetitions (based on 14.2 hours/day median wear time) would be a simple and feasible measure to promote bone health in CCS. Future research should focus on longitudinal or interventional designs in larger cohorts and use

the same analytic approach to assess IL of bone to better quantifying amount, type and pattern of impact loading beneficial to bone health in CCS taking important cancer and bone-specific parameters that may play a role in determining bone health into consideration.

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Contributions/responsibilities are described as follows: SK, NXvdW, CSR: designed the SURfit study; NXvdW, CS, SZ, RJ, CSR, SK: conducted the SURfit study; RJ: analysed Accelerometer data; SM, RJ and SZ analysed pQCT data; SZ: conducted the statistical analyses; SZ, RJ, and SK: interpreted results; SZ, RJ, and SK: wrote the first draft of the manuscript; all authors commented on the manuscript and approved the final version. The first 2 authors□ and the last 3 authors* have a shared first/last authorship.

Conflict of interest: None declared.

Figure 1. Example of an acceleration profile by a hip-worn accelerometer during fast running. Vertical accelerations are shown from which the average number of impact peaks above 2 g per hour (IPN) were calculated. Peaks in negative (e.g. jumping) and positive direction (e.g. landing) were counted because both lead to a compression of lower body bones. The vertical acceleration signal was corrected for gravity such that a value of zero corresponded to standing.

Figure 2. Differences in densitometric and microstructural bone health measures across physical activity groups (reference = lowest group) including Beta and 95% confidence interval. Physical activity groups (low, middle (Mid.) and high) reflect tertiles (physical activity variables were ordered and divided into 3 equally sized groups) based on the different physical activity measures obtained by accelerometry. Shown are average minutes spent in activities above 2 g per day according to Rowlands and Stiles[1] (Impact Peak Duration, IPD), and average number of impact peaks above 2 g per hour (Impact Peak Number, IPN). Shown are 3 models per illustration (from left to right): black bars show unadjusted, dark grey bars muscle mass adjusted, and grey bars the full co-variate adjusted differences (including muscle mass, sex, age, height, age at diagnosis, anthracycline therapy, steroid therapy, cranial radiation ≥24 grey, and smoking status). Additional information can be found in **Supporting Information Tables S3 to S4** (coefficients, confidence intervals, and p-values).

Table 1. Characteristics of childhood cancer survivors (n=161)

Table 2. Prevalence of low bone health by pQCT and DXA in childhood cancer survivors according to sex

Table 3. Characteristics of childhood cancer survivors stratified by physical activity tertile groups according to Impact Loading Duration (IPD) [1]

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Table 1. Characteristics of childhood cancer survivors (n=161)

	n (%)	Median (IQR)
Basic characteristics & health behavior		
Sex, female	72 (45)	
Age (years)	161	28.5 (23.4 ; 36.6)
Smoker, yes	36 (22)	
Muscle mass		
pQCT: tibia 66% muscular CSA (mm²)		
Females	68	5315 (4899 ; 5956)
Males	82	6874 (6002 ; 7467)
DXA: total body lean body mass (kg)		
Females	72	37.9 (34.2 ; 40.9)
Males	85	53.0 (49.9 ; 57.2)
Cancer related information		
Age at diagnosis (yrs.)	161	6.7 (3.2 ; 11.7)
Time since diagnosis (yrs.)	161	22.2 (16.0 ; 29.1)
ICCC-3 cancer diagnoses		
I Leukemia	57 (35)	
II Lymphoma	34 (21)	
III Central nervous system tumor	18 (11)	
IV-XIII Other tumors	52 (32)	
Chemotherapy		
Cumulative anthracycline dose (mg/m²) [1]	91 (57)	180 (120 ; 250)
Cumulative steroid dose (mg/m²) [2]	82 (61)	3410 (2063 ; 4227)
Radiation therapy		
Received cranial radiation therapy	28 (17)	
Cranial radiation dose ≥24 Gy	21 (13)	
Physical activity (accelerometry) [3]	149	
MVPA (min/day)		38.7 (26.1 ; 52.5)
CPM (counts/min)		332.4 (265.2 ; 411.5)
Wear-time: number of days, h/day		11 (8 ; 13), 14.2 (13.5 ; 15.1)
IPD (min >2g/day)		1.17 (0.55 ; 2.34)
Low, middle, high tertile activity group		0.38 (0.24 ; 0.53), 1.18 (0.96 ; 1.54), 2.80 (2.34 ; 3.78)
IPN (number of peaks >2g/h)		3.88 (1.32 ; 11.21)
Low, middle, high tertile activity group		0.85 (0.56 ; 1.29), 3.85 (2.60 ; 4.92), 19.07 (11.21 ; 39.70)

Abbreviations: CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; ICCC-3, International Classification of Childhood Cancer 3rd edition; IQR, interquartile range from 25th to 75th percentile; pQCT, peripheral quantitative computed tomography.

[1] In those who received anthracycline therapy.
[2] In those who received steroid therapy.
[3] Measures of physical activity determined within wear-time period from 6 am to 10 pm by ActiGraph® GT3X+ accelerometer included daily average time (minutes) spent in moderate to vigorous physical activity (MVPA), total physical activity measured by total counts per minute (CPM), average duration spent in impact peaks above 2g per minute and day calculated according to Rowlands and Stiles[1] (IPD), average number of impact peaks above 2g per minute and day (IPN).

Table 2. Prevalence of low bone health by pQCT and DXA in childhood cancer survivors according to sex

Variable	Females z-score ≤ -1		Males z-score ≤ -1	
	n / total [1]	Prevalence	n / total [1]	Prevalence
pQCT z-scores: tibia 4% [2]				
tot vBMD	23 / 70	32,9%	49 / 88	55,7%
trab vBMD	16 / 70	20,5%	18 / 88	20,5%
Any pQCT site [3]	24 / 70	34,3%	49 / 88	55,7%
DXA z-scores [2]				
Femoral neck	19 / 72	26,4%	20 / 84	23,8%
Total hip	12 / 72	16,7%	15 / 84	17,9%
Lumbar spine	20 / 70	28,6%	37 / 85	43,5%
Any DXA site [3]	30 / 72	41,7%	43 / 86	50,0%

Abbreviations: DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; tot vBMD, total volumetric bone mineral density; trab vBMD, trabecular volumetric bone mineral density.

[1] in those with non-missing measurement
[2] z-scores for pQCT according to Roggen et al.[23] and for DXA according to Kelly et al.[25]
[3] pQCT z-score or any DXA z-score ≤ -1, respectively

Table 3. Characteristics of childhood cancer survivors stratified by physical activity tertile groups according to Impact Loading Duration (IPD) [1]

	low IPD tertile (n=49)	middle IPD tertile (n=50)	high IPD tertile (n=50)
	Median (IQR) / count (%)	Median (IQR) / count (%)	Median (IQR) / count (%)
Basic characteristics & health behavior			
Sex, female	26 (53)	20 (40)	20 (40)
Age (years)	27.6 (23.6 ; 33.6)	28.5 (24.3 ; 35.5)	31.8 (24.5 ; 39.3)
Smoker, yes	15 (31)	14 (28)	4 (8)
Muscle mass			
pQCT: tibia 66% muscular CSA (mm^2)			
Females	5249 (4966 ; 5624)	5235 (4478 ; 5600)	5665 (5098 ; 6112)
Males	6732 (5973 ; 7190)	6889 (6109 ; 7441)	6998 (5998 ; 7476)
DXA: total body lean body mass (kg)			
Females	36 (34 ; 40)	36 (34; 40)	39 (38 ; 42)
Males	52 (44 ; 56)	53 (50 ; 56)	55 (52 ; 58)
Cancer related information			
Age at diagnosis (yrs.)	6.4 (3.2 ; 11.8)	5.2 (2.9 ; 11.0)	9.9 (5.4 ; 12.3)
Time since diagnosis (yrs.)	21.8 (15.6 ; 28.3)	23.7 (19.1 ; 30.0)	21.2 (14.6 ; 31.0)
ICCC-3 cancer diagnoses			
I Leukemia	15 (31)	20 (40)	16 (32)
II Lymphoma	10 (20)	8 (16)	16 (32)
III Central nervous system tumor	4 (8)	7 (14)	5 (10)
IV-XIII Other tumors	20 (41)	15 (30)	13 (26)
Chemotherapy			
Cumulative anthracycline dose (mg/m^2) [1]	160 (139 ; 225)	180 (150 ; 240)	150 (100 ; 250)
Cumulative steroid dose (mg/m^2) [2]	3410 (1721 ; 4200)	3410 (2268 ; 3796)	3255 (1968 ; 4982)
Radiation therapy	25 (51)	21 (42)	16 (32)
Received cranial radiation therapy	10 (20)	11 (22)	6 (12)
Cranial radiation dose ≥24 Gy	7 (14)	9 (18)	5 (10)
Treatments and medications			
Physical activity limiting conditions [3]	10 (20)	9 (18)	7 (14)
Contraceptive pill	5 (10)	6 (12)	4 (8)
Regular calcium / vitamin D supplementation	2 (4)	3 (6)	1 (2)
Late puberty [4]	4 (8)	8 (16)	7 (14)
Hypothyroidism	6 (12)	4 (8)	6 (12)

Abbreviations: CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; ICCC-3, International Classification of Childhood Cancer 3rd edition; IQR, interquartile range from 25th to 75th percentile; pQCT, peripheral quantitative computed tomography.

[1] In those who received anthracycline therapy.
[2] In those who received steroid therapy.
[3] Includes those with long-term treatment with immunosuppressant's, and potentially movement & functional limiting conditions (prosthesis, paresis, and spinal deformities).
[4] Includes those with a history of late puberty (e.g. growth hormone deficit, late menstruation).